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SUMMARY

The main function of vitamin D is to increase the calcium absorption from the gut in order to facilitate the mineralization of bone. In the last decades, the number of studies published on other possible consequences of vitamin D increased enormously, resulting in an exponential increase in laboratory requests for serum 25-hydroxyvitamin D (25(OH)D) determination. It is well known that vitamin D deficiency is common in older individuals. The life expectancy is still increasing and therefore the total burden of vitamin D deficiency among the population will also increase. Several risk factors for vitamin D deficiency in the older population have been established. As the main source of vitamin D is the conversion of 7-dehydrocholesterol in the skin under influence of UVB-radiation, a change in lifestyle of the older population, such as less outdoor activities, will increase the risk of vitamin D deficiency. In addition, with increasing age, the skin becomes less efficient in producing vitamin D.

This thesis aimed to better define the determinants and consequences of vitamin D deficiency in the older population in order to stimulate a better vitamin D status in this population group. To reach this aim, data from two different studies were used: two cohorts of the Longitudinal Aging Study Amsterdam (LASA) and the baseline measurement of the B-Vitamins for the PRevention Of Osteoporotic Fractures (B-PROOF) study. LASA is an ongoing cohort study of a representative sample of the Dutch older population; B-PROOF is a multicentre double-blinded placebo-controlled trial on the effects of B-vitamins on the prevention of osteoporotic fractures.

Determinants of vitamin D deficiency

In chapter 2, the association between medication use and serum 25(OH)D concentrations was examined. Data from the two different cohorts of LASA were used. It was found that the use of medication in general was associated with lower serum 25(OH)D and that the number of medicines used was negatively associated with serum 25(OH)D. For several specific medicines, i.e. loop diuretics, inhaled corticosteroids (only in men), oral antidiabetics, calcium channel blockers, and ACE inhibitors, it was shown that users had lower serum 25(OH)D concentrations as compared to non-users. The results of this chapter indicate that the use of medication in general, regardless of type, and several specific medicines may have an impact on vitamin D status and clinicians should be aware of low vitamin D status in case of use of these specific medicines or polypharmacy.

In chapter 3, two models for the prediction of vitamin D deficiency (< 30 nmol/l and < 50 nmol/l) were developed in order to predict low vitamin D status without blood

measurements. Both models consisted of easy assessable variables, which allows health care professionals and individuals themselves to use the models without difficult or time-consuming measurements. The models were able to predict low vitamin D status accurately and the model < 50 nmol/l was successfully validated in an independent cohort. The model < 30 nmol/l could not be validated, because only a few individuals in the validation cohort had levels < 30 nmol/l. The model < 50 nmol/l consisted of 13 parameters: age, sex, body mass index (BMI), smoking habits, alcohol use, season, vitamin tablets use, bicycling, sporting, gardening, medications use, presence of appetite, and partner status. The model < 30 nmol/l consisted of 10 parameters: age, smoking habits, alcohol use, season, vitamin tablets use, bicycling, gardening, medication use, limitations in transport use, and problems with remembering the current years. The developed models can be used by, for example, general practitioners to convince people to take vitamin D supplements, in particular if the model predicts a high risk of vitamin D deficiency. In addition, the models can be used as self-tests hosted on the Internet.

Consequences of vitamin D deficiency

In chapter 4, we examined whether low vitamin D status was associated with physical performance in two different age groups using the three cohorts of both studies. Physical performance was measured by three different tests: the walking test, the chair stand test, and the tandem stand test. Previously it was found that low vitamin D status was associated with physical performance cross-sectionally and longitudinally in individuals aged 65 years and older. In chapter 4, we were able to confirm this cross-sectional relationship in two cohorts. Also, in somewhat younger individuals, aged 55-65 years, low vitamin D status was associated with worse physical performance. However, in this age group, low vitamin D status was not predictive of a decline in physical performance in three and six years time.

In chapter 5, it was studied whether vitamin D status was associated with a subjective measure of physical functioning, i.e. functional limitations. Functional limitations were assessed by asking the participant several questions on the ability to perform six activities of daily life. These activities were: to walk up and down a staircase of 15 steps without resting, to dress and undress oneself, to sit down and stand up from a chair, to cut one's own toenails, to walk outside during 5 minutes without resting and to use one's own or public transportation. In both age groups (55-65 years and > 65 years) low vitamin D status was associated with the presence of functional limitations. When the activities were analysed separately in the older age group, it was found that vitamin D status was only associated with walking stairs, cutting toenails and walking outside. Longitudinally, we

found that low vitamin D status was associated with an increase in limitations in three years in individuals aged 65 years and older, whereas in individuals of 55-65 years, low vitamin D status was associated with an increase in limitations in six years time. The results of chapters 4 and 5, indicate that vitamin D supplements may be of benefit in preventing functional decline, however, this has to be tested in large clinical trials.

In chapter 6, the cross-sectional association of vitamin D status and bone health was studied. Bone health was estimated by measurements with ultrasound (QUS) and dual-energy X-ray absorptiometry (DXA). It was found that BMI modified the association between low vitamin D status and both Broadband Ultrasound Attenuation (one of the parameters of the QUS measurements) and bone mineral density measured by DXA. Only in individuals with low-to-normal BMI, low vitamin D status was associated with lower BUA and BMD. In addition, these associations were found only in the older cohorts (> 65 years).

In chapter 7, it was examined whether vitamin D status was associated with preclinical stages of vascular disease. These preclinical stages were assessed by measuring pulse wave velocity (PWV) by applanation tonometry and carotid intima media thickness (IMT) by ultrasonography. One finding was that the relationships of vitamin D status with IMT and PWV were not linear. Several effect modifiers were tested. These analyses revealed that only in vitamin D sufficient individuals serum 25(OH)D was associated with higher carotid IMT. The association between vitamin D status and PWV was not significant.

Towards an optimal vitamin D status in the older population

The thresholds for serum 25(OH)D are still being debated and in chapter 8, these thresholds were studied with respect to different, also non-skeletal, outcomes and in different subgroups, i.e. men and women, different age and BMI categories. The outcomes that were considered were falling, fractures, parathyroid hormone (PTH), hypertension, cardiovascular disease, blood pressure, grip strength, physical performance, functional limitations, BMI and mortality. For the whole sample, thresholds for serum 25(OH)D ranged from 46 (PTH) to 68 nmol/l (hypertension). Furthermore, it was found that the thresholds vary between the different subgroups. Women, individuals ≥ 75 years of age and individuals with high BMI ($\geq 25 \text{ kg/m}^2$), on average, had lower thresholds compared to men, individuals < 75 years of age and individuals with BMI < 25 kg/m^2 , respectively. Our study was based on observational, and partly cross-sectional data. Therefore, these thresholds have to be validated in clinical trials that incorporate different subgroups.

In chapter 9, a report of a national expert meeting was given. During this national expert meeting, a strategy for a better implementation of the current advice of the Dutch Health Council on vitamin D supplementation was developed. It was suggested that existing

contact moments with health care professionals need to be used for dissemination of the advice. The children's health clinic can be used to inform the whole family about vitamin D supplementation. Polypharmacy evaluation moments, the screening for mamma carcinoma and the flu vaccination can also be used to disseminate the advice. Because not all risk groups can be reached at the same time, prioritizing is necessary. Based on the current evidence for the effectiveness of supplementation, the urgency and reachability, first the institutionalized individuals should be aimed at, and second the independent living older individuals and finally the non-western immigrants.

Discussion and conclusion

In chapter 10, the most important results and methodological considerations of the studies presented in this thesis were discussed. It was concluded that medication use is associated with low vitamin D status and that vitamin D status can be predicted by simple patient characteristics. Furthermore, low vitamin D status is associated with physical functioning, both cross-sectionally and longitudinally; with worse bone health, only in individuals with low-to-normal BMI; and with higher IMT in vitamin D sufficient individuals. Thresholds for serum 25(OH)D were estimated and women, individuals ≥ 75 years and individuals with high BMI have lower thresholds compared to men, < 75 years and low-to-normal BMI. Lastly, a strategy to better implement the current advice of the Dutch Health Council was proposed. Although this thesis showed some interesting associations on determinants and consequences of vitamin D status, definite conclusions on a causal relationship could not be drawn. Large clinical trials, with long follow-up times and adequate doses of vitamin D are necessary. Several of such clinical trials are currently undertaken. The results will become available in the next years.